IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Karin DRECHSEL, et al. Examiner: Mina Haghighatian

Serial No.: 10/735,959 Group Art Unit: 1616

Filed: December 15, 2003

Title: INHALABLE FORMULATION OF A SOLUTION CONTAINING A TIOTROPIUM SALT

BRIEF ON APPEAL UNDER 37 C.F.R. §41.37

Sir:

This is an appeal from the decision of the Examiner finally rejecting claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95 of the above-identified application. A Notice of Appeal was filed on April 19, 2010.

(i) REAL PARTY IN INTEREST

The application is assigned of record to BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG, who is the real party in interest herein.

(ii) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee point out that the issues in an appeal filed concurrently with this one in US Ser. No. 10/392,558 are related. Appellants, their legal representative and the assignee are not aware of any other related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(iii) STATUS OF THE CLAIMS

Claims rejected:	Claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95.
Claims allowed:	(none)
Claims canceled:	Claims 15, 17, 21, 32-37, 67 and 69.
Claims withdrawn:	(none)

Claims on Appeal: Claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95 (Copy of claims on appeal in attached Appendix).

(iv) STATUS OF AMENDMENTS

No amendments after the Final Rejection have been proposed by Appellants.

(v) SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' invention (independent claim 1) is directed to a propellant-free pharmaceutical composition (see, e.g., page 1, lines 11-13, of the specification). The composition comprises:

(a) an active substance comprising tiotropium or a pharmaceutically acceptable salt thereof, in a concentration based on tiotropium of between 0.0005 and 5% by weight (see, e.g., page 1, line 23, to page 2, line 8, and page 5, lines 20-26, of the specification);

(b) a solvent selected from water and water/ethanol mixture (see, e.g., page 5, lines 8-13, of the specification);

(c) acid for achieving a pH of from 2.5 and 3.0 (see, e.g., page 5, lines 28-30, page 6, lines 1-3, and Table 1, page 16, of the specification);

(d) a pharmacologically acceptable preservative (see, e.g., page 8, lines 9-12, of the specification); and

(e) a complexing agent comprising edetic acid or an edetic acid salt in an amount from greater than 0 to 25 mg per 100 mL (see, e.g., page 6, line 21, to page 7, line 2, of the specification),

optionally including a stabilizer, a pharmacologically acceptable cosolvent, or other pharmacologically acceptable adjuvants and additives but containing no propellant; and wherein the amount of edetic acid or an edetic acid salt results in a reduction in the incidence of spray anomalies (see, e.g., page 7, line 23, to page 8, line 3, and the original claims of the specification).

Appellants' invention (independent claim 31) is directed to a pharmaceutical composition comprising water, 0.1% by weight of tiotropium bromide, 0.01% by weight of benzalkonium chloride, and 0.05% by weight of sodium edetate, which is adjusted to a pH of 3.0 using hydrochloric acid (see, e.g., original claim 31, page 20, of the specification).

Appellants' invention (independent claim 53) is directed to a propellant-free pharmaceutical composition comprising:

(a) an active ingredient consisting essentially of a tiotropium salt, in a concentration based on tiotropium of between 0.0005 and 5% by weight (see, e.g., page 1, line 23, to page 2, line 8, and page 5, lines 20-26, of the specification);

(b) a solvent selected from water or a water/ethanol mixture (see, e.g., page 5, lines 8-13, of the specification);

(c) acid for achieving a pH of from 2.5 to 3.0 (see, e.g., page 5, lines 28-30, page 6, lines 1-3, and Table 1, page 16, of the specification);

(d) a pharmacologically acceptable preservative (see, e.g., page 8, lines 9-12, of the specification); and

(e) a complexing agent comprising edetic acid or an edetic acid salt in an amount of from greater than 0 to 25 mg/100 mL (see, e.g., page 6, line 21, to page 7, line 2, of the specification),

optionally including a stabilizer, a pharmacologically acceptable cosolvent, or other pharmacologically acceptable adjuvants and additives but containing no propellant; and wherein the amount of edetic acid or an edetic acid salt results in a reduction in the incidence of spray anomalies (see, e.g., page 7, line 23, to page 8, line 3, and the original claims of the specification).

(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following outstanding grounds of rejection are requested to be reviewed on appeal. For each ground, any separate consideration of the claims subject to that rejection is indicated.

1. The rejection of claims 1-14, 16, 18-20, 22-31, 50, 53-66, 68, 70-80 and 93 under 35 U.S.C. §103, for allegedly being obvious from Freund (DE 19653969, as evidenced by U.S. 2001/0008632, "Freund '632") in view of Freund (WO 97/01329, translation by US 6,491,897, "Freund '897").

2. The rejection of claims 38-49, 51-52, 81-92, 94 and 95 under 35 U.S.C. §103, for allegedly being obvious from Freund (DE 19653969, as evidenced by U.S. 2001/0008632, "Freund '632") in view of Freund (WO 97/01329, translation by US 6,491,897, "Freund '897") and further in view of Weston (WO 9114468).

3. The provisional rejection of claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95 for obviousness-type double patenting over copending application, Ser. No. 11/068,134.

4. The provisional rejection of claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95 for obviousness-type double patenting over copending application, Ser. No. 10/392,558.

5. The provisional rejection of claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95 for obviousness-type double patenting over copending application, Ser. No. 12/201,149.

6. The provisional rejection of claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95 for obviousness-type double patenting over copending application, Ser. No. 11/006,940.

(vii) ARGUMENT

1. Claims 1-14, 16, 18-20, 22-31, 50, 53-66, 68, 70-80 and 93, on appeal, are not obvious to one of ordinary skill in the art over Freund (DE 19653969, as evidenced by U.S. 2001/0008632, "Freund '632") in view of Freund (WO 97/01329, translation by US 6,491,897, "Freund '897"); thus, the rejection under 35 U.S.C. §103 should be reversed.

Freund '632 discloses pharmaceutical aqueous solutions for providing propellant-free aerosols for inhalation devices; see, e.g., page 1, para. 0001. Amongst the active ingredients for the compositions is included tiotropium bromide. The Freund '632 compositions are characterized by their content of an effective quantity of a complexing agent, particularly sodium edetate; see, e.g., page 1, paras. 0009 – 0013. The effective quantity of the

complexing agent is broadly disclosed as between 10 – 1000 mg/100ml solution. However, it is especially preferred that the amount be 25 -75, more particularly 25-50, mg/100ml solution; see page 1, para. 0013, and page 3, para. 0053. The compositions further contain a preservative such as benzalkonium chloride; see page 1, para. 0010. Freund '632 discloses that its compositions have a pH of 3.2 to 3.4; see page 3, para. 0055.

Freund '632 fails to disclose compositions which contain an acid for adjusting the pH to from 2.5 to 3.0 (see part (c) of claims 1 and 53 and the 3.0 recitation in claim 31). Also Freund '632 fails to specifically direct one of ordinary skill in the art to compositions which contain sodium edetate in an amount of from 0 to 25 mg per 100 ml of the composition (see part (e) of claims 1 and 53). Despite its generic disclosure regarding the amount of sodium edetate, Freund '632 clearly directs one of ordinary skill in the art to compositions which contain a higher amount of sodium edetate, i.e., an amount of 25 mg per 100 ml or higher. As discussed further below, Freund '632 certainly fails to disclose that there would be an advantage to providing compositions which combine the features of using an acid for adjusting the pH to from 2.5 to 3.0 and having a sodium edetate content of from 0 to 25 mg per 100 ml of the composition.

Freund '897 discloses ethanolic solutions of budesonide (a steroid) for use in nebulizer inhalation devices; see the Abstract. Freund '897 provides more general teachings regarding the active agent and other components of its compositions in its disclosure. Freund '897 discloses that its compositions may contain a complex forming agent such as EDTA (edetate) but the amount of such agent is small, only about 0.1 to 3.0 mg/100 ml maximum; see, e.g., col. 3, lines 1-8. Freund '897 discloses that the compositions can contain an acid to adjust the pH in the range from 2.0 to 7.0, especially 3.0 to 4.0; see, e.g., col. 3, lines 60-67. However, in all of the Examples of Freund '897, the pH of the solutions is 3.2 or higher.

Appellants urge that there is no convincing reason why one of ordinary skill in the art would combine the teaching of Freund '897 regarding a broader pH range with Freund '632 to suggest a composition meeting the elements of the instant claims. Freund '632 specifically teaches that the pH of its compositions be 3.2 to 3.4. Thus, its compositions do not generically overlap with the claimed compositions and one of ordinary skill in the art would have to have a reason for modifying the reference. The Freund '897 patent does not provide any sufficient reason for a person of ordinary skill in the art to controvert the express teachings in Freund '632 that its compositions be in the pH range of 3.2 – 3.4. Further, one of ordinary skill in the art would not have reason to apply the broader pH teaching of Freund '897 to the Freund '632 compositions, because the two references relate to distinct types of

compositions. The Freund '897 invention, as stated in the abstract, claims and examples, is directed to steroid compositions, with either flunisolide hemihydrate or budesonide, and not to tiotropium salt compositions. The pH values exemplified for the steroid compositions in Freund '897 examples range from 3.2 -- 7.0 (see Tables II, III and IV). The amount of complexing agent used in the Freund '897 compositions is much less than the amount used in the Freund '632 compositions, which is the primary characterizing feature of the Freund '632 invention. Further, a primary teaching of Freund '897 is to use all or mostly all ethanol solvent for its compositions, whereas, water is the primary solvent of the Freund '632 compositions. The differences between the Freund '897 compositions and the Freund '632 compositions are such that one of ordinary skill in the art would not have had a reason to adjust the pH taught for the Freund '632 by the teachings regarding pH in Freund '897 which relate to compositions which are distinct in several aspects. Freund '632 requires the very specific range of 3.2 to 3.4 pH selected particular for its compositions having a particularly selected combination of components. One of ordinary skill in the art would not alter such very specific teaching regarding pH based on Freund '897 which relates to compositions having a very different combination of components.

For all of the above reasons, it is urged that the combined teachings of the prior art, as a whole, fail to render the invention of the claims on appeal obvious to one of ordinary skill in the art.

Additionally, appellants have provided on the record evidence of the unexpected advantage and nonobviousness of the claimed invention; see the attached Evidence Appendix. The evidence on the decomposition of tiotropium bromide at different pH values demonstrates that the selection of a specific pH range is critical for these tiotropium bromide compositions. This fact is wholly unrecognized in the cited references. The further Attachment evidence demonstrates the nexus between the combined feature of the lower sodium edetate content and lower pH range recited in the claims and the advantageous absence of spray anomalies. The claims are commensurate in scope with this data as to the sodium edetate content and pH. Table 1 of Freund '632 shows tests for determining spray anomalies when the EDTA (edetate) content is modified. Initially, it should be pointed out that Table 1 of Freund '632 relates to ipratropium bromide solutions at 3.4 pH (see para. 0048 of Freund '632), not tiotropium salt solutions in the claimed pH range of 2.7 to 3.1. In any event, one of ordinary skill in the art observing the trend in Table 1 of Freund '632 – and not having the benefit of appellants' inventive contribution showing the advantage of combining

lower sodium edetate and lower pH – could not have expected from the reference that a tiotropium bromide solution at pH 2.7 – 3.1 and a lower sodium edetate amount would lead to less occurrence of spray anomalies. To the contrary, Table 1 of Freund '632 shows that anomalies occur when the lower amounts of sodium edetate tested by Freund were used. Only at the higher amounts, i.e., 50 mg/100 ml and higher, are anomalies avoided. The table in para. 0051 of Freund '632 further evidences that an EDTA amount of 50 mg/100 ml or more is being taught by Freund '632. That appellants' evidence shows avoidance of anomalies at lower pH and lower sodium edetate amount, i.e., at 10 and 25 mg/100 ml is, thus, unexpected in view of Freund '632 and further proof of the nonobviousness of the invention as currently claimed.

Freund '632 provides no suggestion regarding the pH sensitivity of tiotropium bromide in these compositions or that, combining the lower pH and lower sodium edetate amount, an advantageous avoidance of spray anomalies can be achieved. Freund '632 explicitly teaches a general pH range of 3.2 to 3.4 (page 3, para. 0055) and gives no hint of any advantage for using a lower pH. Freund '632, thus, certainly fails to teach compositions with a pH adjusted to "from 2.5 to 3.0." Freund '632 further fails to teach any advantage for a lower sodium edetate amount, as recited in the instant claims. Despite the general disclosure in Freund '632 (para. 0013) that amounts from 10 to 1000 mg/100ml Na-EDTA can be used, the data as discussed above shows a failure to appreciate that amounts lower than 50 mg/100 ml could be used (when combined with the lower pH) to avoid anomalies.

The generic teaching in Freund '897 that compositions with a pH to between 2.0 and 7.0 can be provided fails to provide any expectation to one of ordinary skill in the art that, by combining the specific lower pH range of 2.5 to 3.0 and lower sodium edetate amount, as currently claimed, an advantageous avoidance of spray anomalies can be achieved. Thus, the combined teachings of the cited references fails to refute appellants' showing of nonobviousness and, in light of said showing, fails to render the claimed invention obvious.

The cited prior art as a whole fails to provide any valid reason why one of ordinary skill in the art would modify the teachings of Freund '632 in the manner necessary to arrive at the claimed invention and/or achieve the unexpected advantages of the claimed invention. Even if the prior art teachings are all combined, they merely provide broad ranges which give no hint to the advantageous combination of selections which forms the basis of the claimed invention. Further, the broad pH ranges recited in the secondary reference gives no basis for one of ordinary skill in the art to modify the specific 3.2 - 3.4 range explicitly required by

Freund '632. There would be no rational reason for one of ordinary skill in the art to modify the Freund '632 compositions based on broad teachings in a reference related to different types of compositions when Freund '632 gives an explicit teaching for the pH, specifically optimized for its particular compositions. Rejections on obviousness must be based on some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness (see, e.g., *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740-41, 82 USPQ2d 82 USPQ2d 1385, 1396 (2007); *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006); and MPEP § 2141) and such is not provided on the record here.

For all of the above reasons, the cited references taken alone or in combination do not teach, suggest, or make obvious the present invention to one of ordinary skill in the art. Thus, the rejection under 35 U.S.C. §103 should be reversed.

2. Claims 38-49, 51-52, 81-92, 94 and 95, on appeal, are not obvious to one of ordinary skill in the art from Freund (DE 19653969, as evidenced by U.S. 2001/0008632, "Freund '632") in view of Freund (WO 97/01329, translation by US 6,491,897, "Freund '897") and further in view of Weston (WO 9114468); thus, the rejection under 35 U.S.C. §103 should be reversed.

The discussions of the Freund references in Issue 1 above is incorporated by reference. To summarize, this combination of references, when viewed in light of the evidence of record, fails to render the claimed compositions obvious to one of ordinary skill in the art. Weston teaches a particular type of inhaler and is relied upon merely to suggest that the compositions of the primary references or compositions obvious therefrom could be administered using such an inhaler. Such a combination, however, would not result in or suggest the invention of these claims because the primary references fail to render the claimed compositions obvious. Using compositions taught or rendered obvious by the primary references in the Weston inhaler will not result in the claimed invention because the compositions are be distinct for the reasons discussed above Weston provides no teachings which make up for the above-discussed deficiencies of the primary references to teach or suggest the claimed compositions.

For all of the above reasons, the cited references taken alone or in combination do not teach, suggest, or make obvious the present invention to one of ordinary skill in the art. Thus, the rejection under 35 U.S.C. §103 should be reversed.

3. The provisional obviousness-type double patenting rejection over copending

application, Ser. No. 11/068,134, is moot.

Co-pending application number 11/068,134 was abandoned effective June 3, 2010, and no continuing application therefrom was filed. Thus, the provisional rejection of claims 1-4 and 6-21 for obviousness-type double patenting is rendered moot.

4. The provisional obviousness-type double patenting rejection over copending application, Ser. No. 10/392,558, should be reversed.

According to MPEP 804(I)(B)(1), "if a provisional nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer." The copending application has an effective US filing dates after the earliest effective filing date of the present application and qualifies as a "later-filed" application. Should this manner of provisional double patenting rejection be the only remaining rejections in this application, the practice requires that they be withdrawn. Thus, for example, terminal disclaimers are not necessary for allowance and patenting of the present claims. Thus, the provisional rejections should be reversed.

5. The provisional obviousness-type double patenting rejection over copending application, Ser. No. 12/201,149, should be reversed.

According to MPEP 804(I)(B)(1), "if a provisional nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer." The copending application has an effective US filing dates after the earliest effective filing date of the present application and qualifies as a "later-filed" application. Should this manner of provisional double patenting rejection be the only remaining rejections in this application, the practice requires that they be withdrawn. Thus, for example, terminal disclaimers are not necessary for allowance and patenting of the present claims. Thus, the provisional rejections should be reversed.

6. The provisional obviousness-type double patenting rejection over copending

application, Ser. No. 11/006,940, should be reversed.

According to MPEP 804(I)(B)(1), "if a provisional nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer." The copending application has an effective US filing dates after the earliest effective filing date of the present application and qualifies as a "later-filed" application. Should this manner of provisional double patenting rejection be the only remaining rejections in this application, the practice requires that they be withdrawn. Thus, for example, terminal disclaimers are not necessary for allowance and patenting of the present claims. Thus, the provisional rejections should be reversed.

For all of the above reasons, it is urged that the decision of the Examiner rejecting claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95, on appeal, is in error and should be reversed.

Respectfully submitted,

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JAS:klb

(viii) CLAIMS APPENDIX

1. A propellant-free pharmaceutical composition comprising:

(a) an active substance comprising tiotropium or a pharmaceutically acceptable salt thereof, in a concentration based on tiotropium of between 0.0005 and 5% by weight;

(b) a solvent selected from water or a water/ethanol mixture;

(c) acid for achieving a pH of from 2.5 to 3.0;

(d) a pharmacologically acceptable preservative; and

(e) a complexing agent comprising edetic acid or an edetic acid salt in an amount from greater than 0 to 25 mg/100 mL,

optionally including a stabilizer, a pharmacologically acceptable cosolvent, or other pharmacologically acceptable adjuvants and additives but containing no propellant; and wherein the amount of edetic acid or an edetic acid salt results in a reduction in the incidence of spray anomalies.

2. The pharmaceutical composition according to claim 1, wherein the tiotropium salt is selected from the group consisting of salts with a bromide, chloride, iodide, monomethylsulphate, methanesulphonate and/or p-toluenesulphonate anion.

3. The pharmaceutical composition according to claim 1, wherein the active substance is tiotropium bromide.

4. The pharmaceutical composition according to claim 1, wherein the active substance is tiotropium bromide monohydrate.

5. The pharmaceutical composition according to claim 1, wherein the solvent is water.

6. The pharmaceutical composition according to claim 2, wherein the solvent is water.

7. The pharmaceutical composition according to claim 3, wherein the solvent is water.

8. The pharmaceutical composition according to claim 4, wherein the solvent is water.

9. The pharmaceutical composition according to claim 1, wherein the solvent is a water-ethanol mixture with up to 70 vol.% of ethanol.

10. The pharmaceutical composition according to claim 2, wherein the solvent is a water-ethanol mixture with up to 70 vol.% of ethanol.

11. The pharmaceutical composition according to claim 3, wherein the solvent is a water-ethanol mixture with up to 70 vol.% of ethanol.

12. The pharmaceutical composition according to claim 4, wherein the solvent is a water-ethanol mixture with up to 70 vol.% of ethanol.

13. The pharmaceutical composition according to claim 9, wherein the solvent is a water-ethanol mixture with up to 60 vol.% of ethanol.

14. The pharmaceutical composition according to claim 13, wherein the solvent is a water-ethanol mixture with up to 30 vol.% of ethanol.

16. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition does not contain a stabilizer.

18. The pharmaceutical composition according to claim 1, wherein the edetic acid salt is present in an amount of from 5 to 10 mg/100 ml.

19. The pharmaceutical composition according to claim 1, wherein the edetic acid salt is sodium edetate.

22. The pharmaceutical composition according to claim 1, wherein the pH is from 2.7 to 3.0.

23. The pharmaceutical composition according to claims 1, wherein the concentration based on tiotropium is between 0.001% and 3% by weight.

24. The pharmaceutical composition according to claim 23, wherein the concentration based on tiotropium is between 0.0005% to 0.5% by weight.

25. The pharmaceutical composition according to claim 24, wherein the concentration based on tiotropium is between 0.0005% to 0.25% by weight.

26. The pharmaceutical composition according to claim 25, wherein the concentration based on tiotropium is between 0.001% to 0.1% by weight.

27. The pharmaceutical composition according to claim 1, wherein the pharmacologically acceptable preservative is benzalkonium chloride.

28. The pharmaceutical composition according to claims 1, wherein the pharmaceutical composition comprises a pharmacologically acceptable adjuvant or additive.

29. The pharmaceutical composition according to claim 28, wherein pharmacologically acceptable adjuvant or additive is an antioxidant.

30. The pharmaceutical composition according to claims 1, wherein the pharmaceutical composition contains no cosolvents and/or pharmacologically acceptable adjuvants and additives apart from the preservative.

31. A pharmaceutical composition comprising water, 0.1% by weight of tiotropium bromide, 0.01% by weight of benzalkonium chloride, and 0.05% by weight of sodium edetate, which is adjusted to a pH of 3.0 using hydrochloric acid.

38. (Currently amended) A method for administering a pharmaceutical composition according to claim 1, comprising nebulizing the pharmaceutical composition in an inhaler selected from the group consisting of: (a) an inhaler according to the Weston Nebulizer, or (b) an inhaler according to the Jaeger Nebulizer B.

39. A method for administering a pharmaceutical composition according to claim 1, comprising nebulizing the pharmaceutical composition in an inhaler which nebulizes defined amounts of the pharmaceutical composition by the application of pressures from 100 to 600 bar through a nozzle having at least one nozzle opening with a depth of 2 to 10 microns and a width of 5 to 15 microns to form an inhalable aerosol.

40. The method according to claim 39, wherein at least one nozzle opening is at least two nozzle openings which are inclined relative to one another in the direction of the nozzle opening at an angle of from 20 degrees to 160 degrees.

41. The method according to claim 39, wherein the defined amounts of the pharmaceutical composition are 10 to 50 microliters.

42. The method according to claim 38, wherein the inhaler is 9 cm to 15 cm long and 2 cm to 4 cm wide.

43. The method according to claim 39, wherein the inhaler is 9 cm to 15 cm long and 2 cm to 4 cm wide.

44. The method according to claim 38, wherein the mass of pharmaceutical composition delivered in at least 97% of all actuations of the inhaler is between 5 mg and 30 mg within a range of tolerance of 25%.

45. The method according to claim 39, wherein the mass of pharmaceutical composition delivered in at least 97% of all actuations of the inhaler is between 5 mg and 30 mg within a range of tolerance of 25%.

46. The method according to claim 38, wherein the mass of pharmaceutical composition delivered in at least 97% of all actuations of the inhaler is between 5 mg and 30 mg within a range of tolerance of 20%.

47. The method according to claim 39, wherein the mass of pharmaceutical composition delivered in at least 97% of all actuations of the inhaler is between 5 mg and 30 mg within a range of tolerance of 20%.

48. The method according to claim 38, wherein the mass of pharmaceutical composition delivered in at least 98% of all actuations of the inhaler is between 5 mg and 30 mg within a range of tolerance of 20%.

49. The method according to claim 39, wherein the mass of pharmaceutical composition delivered in at least 98% of all actuations of the inhaler is between 5 mg and 30 mg within a range of tolerance of 20%.

50. A method of treating asthma or COPD in a patient, the method comprising administering to the patient a pharmaceutical composition according to claim 1.

51. A method of treating asthma or COPD in a patient, the method comprising administering to the patient a pharmaceutical composition using the method of claim 38.

52. A method of treating asthma or COPD in a patient, the method comprising administering to the patient a pharmaceutical composition using the method of claim 39.

53. A propellant-free pharmaceutical composition comprising:

(a) an active ingredient consisting essentially of a tiotropium salt, in a concentration based on tiotropium of between 0.0005 and 5% by weight;

(b) a solvent selected from water or a water/ethanol mixture;

(c) acid for achieving a pH of from 2.5 to 3.0;

(d) a pharmacologically acceptable preservative; and

(e) a complexing agent comprising edetic acid or an edetic acid salt in an amount of from greater than 0 to 25 mg/100 mL,

optionally including a stabilizer, a pharmacologically acceptable cosolvent, or other pharmacologically acceptable adjuvants and additives but containing no propellant; and wherein the amount of edetic acid or an edetic acid salt results in a reduction in the incidence of spray anomalies.

54. The pharmaceutical composition according to claim 53, wherein the tiotropium salt is selected from the group consisting salts with a bromide, chloride, iodide, monomethylsulphate, methanesulphonate and/or p-toluenesulphonate anion.

55. The pharmaceutical composition according to claim 53, wherein the tiotropium salt is tiotropium bromide.

56. The pharmaceutical composition according to claim 53, wherein the tiotropium salt is tiotropium bromide monohydrate.

57. The pharmaceutical composition according to claim 53, wherein the solvent is water.

58. The pharmaceutical composition according to claim 54, wherein the solvent is water.

59. The pharmaceutical composition according to claim 55, wherein the solvent is water.

60. The pharmaceutical preparation composition according to claim 56, wherein the solvent is water.

61. The pharmaceutical composition according to claim 53, wherein the solvent is a water-ethanol mixture with up to 70 vol.% of ethanol.

62. The pharmaceutical composition according to claim 54, wherein the solvent is a water-ethanol mixture with up to 70 vol.% of ethanol.

63. The pharmaceutical composition according to claim 55, wherein the solvent is a water-ethanol mixture with up to 70 vol.% of ethanol.

64. The pharmaceutical composition according to claim 56, wherein the solvent is a water-ethanol mixture with up to 70 vol.% of ethanol.

65. The pharmaceutical composition according to claim 61, wherein the solvent is a water-ethanol mixture with up to 60 vol.% of ethanol.

66. The pharmaceutical composition according to claim 65, wherein the solvent is a water-ethanol mixture with up to 30 vol.% of ethanol.

68. The pharmaceutical composition according to claim 53, wherein the pharmaceutical composition does not contain a stabilizer.

70. The pharmaceutical composition according to claim 53, wherein the edetic acid salt is sodium edetate.

72. The pharmaceutical composition according to claim 53, wherein the pH is from 2.7 to 3.0.

73. The pharmaceutical composition according to claim 53, wherein the concentration based on tiotropium is between 0.001% and 3% by weight.

74. The pharmaceutical composition according to claim 73, wherein the concentration based on tiotropium is between 0.0005% to 0.5% by weight.

75. The pharmaceutical composition according to claim 74, wherein the concentration based on tiotropium is between 0.0005% to 0.25% by weight.

76. The pharmaceutical composition according to claim 75, wherein the concentration based on tiotropium is between 0.001% to 0.1% by weight.

77. The pharmaceutical composition according to claim 53, wherein the pharmacologically acceptable preservative is benzalkonium chloride.

78. The pharmaceutical composition according to claim 53, wherein the pharmaceutical composition comprises a pharmacologically acceptable adjuvant or additive.

79. The pharmaceutical composition according to claim 78, wherein pharmacologically acceptable adjuvant or additive is an antioxidant.

80. The pharmaceutical composition according to claim 53, wherein the pharmaceutical composition contains no cosolvents and/or pharmacologically acceptable adjuvants and additives apart from the preservative.

81. A method for administering a pharmaceutical composition according to claim 53, comprising nebulizing the pharmaceutical composition in an inhaler selected from the group consisting of: (a) an inhaler according to the Weston Nebulizer, or (b) an inhaler according to the Jaeger Nebulizer B.

82. A method for administering a pharmaceutical composition according to claim 53, comprising nebulizing the pharmaceutical composition in an inhaler which nebulizes defined amounts of the pharmaceutical composition by the application of pressures from 100 to 600 bar through a nozzle having at least one nozzle opening with a depth of 2 to 10 microns and a width of 5 to 15 microns to form an inhalable aerosol.

83. The method according to claim 82, wherein at least one nozzle opening is at least two nozzle openings which are inclined relative to one another in the direction of the nozzle opening at an angle of from 20 degrees to 160 degrees.

84. The method according to claim 82, wherein the defined amounts of the pharmaceutical composition are 10 to 50 microliters.

85. The method according to claim 81, wherein the inhaler is 9 cm to 15 cm long and 2 cm to 4 cm wide.

86. The method according to claim 82, wherein the inhaler is 9 cm to 15 cm long and 2 cm to 4 cm wide.

87. The method according to claim 81, wherein the mass of pharmaceutical composition delivered in at least 97% of all actuations of the inhaler is between 5 mg and 30 mg within a range of tolerance of 25%.

88. The method according to claim 82, wherein the mass of pharmaceutical composition delivered in at least 97% of all actuations of the inhaler is between 5 mg and 30 mg within a range of tolerance of 25%.

89. The method according to claim 81, wherein the mass of pharmaceutical composition delivered in at least 97% of all actuations of the inhaler is between 5 mg and 30 mg within a range of tolerance of 20%.

90. The method according to claim 82, wherein the mass of pharmaceutical composition delivered in at least 97% of all actuations of the inhaler is between 5 mg and 30 mg within a range of tolerance of 20%.

91. The method according to claim 81, wherein the mass of pharmaceutical composition delivered in at least 98% of all actuations of the inhaler is between 5 mg and 30 mg within a range of tolerance of 20%.

92. The method according to claim 82, wherein the mass of pharmaceutical composition delivered in at least 98% of all actuations of the inhaler is between 5 mg and 30 mg within a range of tolerance of 20%.

93. A method of treating asthma or COPD in a patient, the method comprising administering to the patient a pharmaceutical composition according to claim 53.

94. A method of treating asthma or COPD in a patient, the method comprising administering to the patient a pharmaceutical composition using the method of claim 81.

95. A method of treating asthma or COPD in a patient, the method comprising administering to the patient a pharmaceutical composition using the method of claim 82.

(ix) EVIDENCE APPENDIX

An appendix containing copies of evidence considered and entered by the examiner and relied upon by appellant in the appeal, along with a statement setting forth where in the record that evidence was entered in the record by the examiner is provided.

1. Data on Decomposition of tiotropium bromide at different pH values submitted with Reply filed November 3, 2005. Considered by Examiner in Office action of February 28, 2006.

2. Attachment: Experimental Findings on Spray Quality of Formulations submitted with Reply filed April 21, 2008. Considered by Examiner in Office action of August 14, 2008.

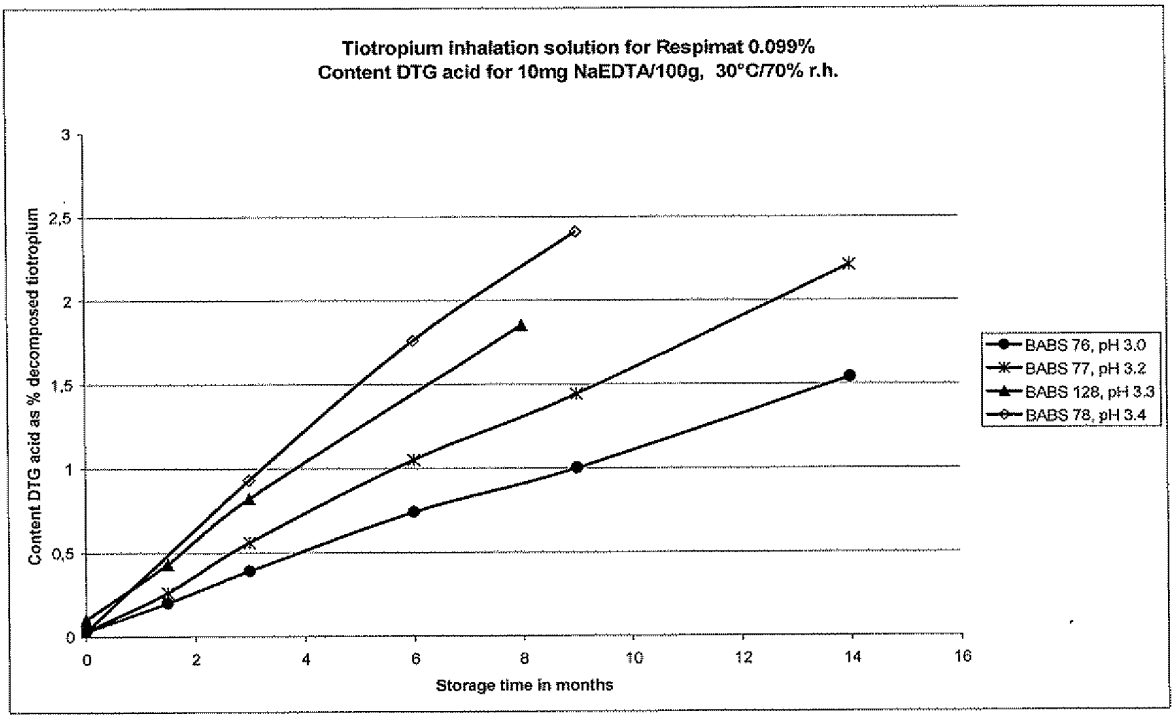
(x) RELATED PROCEEDINGS APPENDIX

(None)

Data on Decomposition of tiotropium bromide at different pH values submitted with Reply filed July 9, 2007.

Aqueous formulations containing 0.099% tiotropium, 10mg/100ml sodium edentate and 10mg/100ml benzalkonium chloride were adjusted with HCl to pH values of 3.0, 3.2, 3.3 and 3.4, respectively, and stored at 30°C/70% r.h. Thereafter, the decomposition of tiotropium was measured by determining content of decomposition product dithienyl-glycolic acid (DTG acid). The results for the 4 different formulations are summarized in the diagram below.

Decomposition of tiotropium bromide at different pH values:



Surprisingly, it has been found that stability of tiotropium bromide in the range of 3.0 to 3.4 is strongly pH dependent, whereas, at pH of 3.0, the tiotropium solutions are relatively stable. Quicker degradation is seen at pH levels of 3.2, thereby leading to a larger amount of DTG acid.

ATTACHMENT: Experimental findings concerning spray quality of formulations

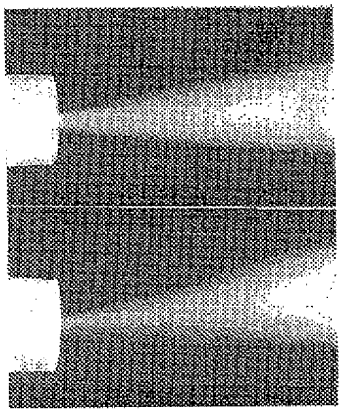
I. Composition of the investigated solutions:

Tiotropium	NaEDTA	BACl	Purified water ad	pH value
0.099 mg	50 mg	10 mg	100 g	2.7
				3.0
				3.1
				3.2
	25 mg			2.7
				2.8
				3.0
				3.1
				3.2
	10 mg			2.7
				2.8
				3.0
				3.1
				3.2
	0 mg			2.7
				3.3

The dosage 0.099mg relates to tiotropium. 1 mg tiotropium corresponds to 1.2495 mg tiotropium bromide;

"BACl" is Benzalkonium chloride;

II. Determination of spray quality:
For assessment of the spray quality the devices were sprayed under a cold light lamp over black paper into a vent. The evaluation was performed visually. The following picture describes a spray generated normally:



III. Results:

The following table gives an overview of actuations that were to be classified as sprays with deviations from the typical spray pattern in dependency from the chosen formulation:

pH value	NaEDTA [mg/100g]	Sprays with deviation			
		Devices		Actuations	
		abs.	rel. [%]	abs.	rel. [%]
2.7	0	0	0	0	0
	10	0	0	0	0
	25	1	2.6	1	0.01
	50	28	70.0	2667	17.10
2.8	10	0	0	0	0
	25	2	5.0	11	0.07
3.0	10	1	2.5	1	0.01
	25	0	0	0	0
	50	5	12.5	13	0.08
3.1	10	1	2.5	1	0.01
	25	1	2.5	1	0.01
	50	2	5.0	2	0.01
3.2	10	0	0	0	0
	25	1	2.5	1	0.01
	50	2	5.0	3	0.02
3.3	0	0	0	0	0

An improvement of spray quality at lower pH values (pH 2.7-3.0) in combination with lower NaEDTA concentrations (10 and 25 mg) is observed. Formulations with 10 and 25 mg Na EDTA in pH range of 2.7 to 3.2 show not more than 0.1% of all actuations to be classified as sprays with deviations from the typical spray pattern.